Remarks

I. Status

Claims 1-91 have been cancelled in favor of claims 92-132. The Examiner has indicated that claims 93-95, 102-104 and 115-132 have been withdrawn from consideration as directed to a non-elected species. Applicants respectfully submit that claims 98 and 107 appear also to be directed to non-elected species, and accordingly have also been withdrawn. New claims 133-146 have been added. Accordingly, claims 92, 96-97, 99-101, 105-106, 108-114 and 133-146 are presently under Examination.

The Specification has been amended to correct typographical errors. New claims 133-146 are directed to the embodiments in which the amino acid modification at position 396 is a substitution of leucine at that position. Such claims are fully supported by the specification (see, e.g., Tables 2-5). No new matter has been added by any of the requested amendments.

II. The Election of Species Requirement

The Examiner has advised that the claims are directed to two patentably distinct species of claimed inventions:

Group (A) polypeptides comprising a variant Fc region, wherein said Fc region differs from a wild-type Fc region by comprising at least an amino acid modification at position 396 and ***without*** comprising additional amino acid modifications; or

Group (B) polypeptides comprising a variant Fc region, wherein said Fc region differs from a wild-type Fc region by comprising at least an amino acid modification at position 396 and ***further comprising*** additional amino acid modifications,

On April 11, 2007, Applicants provisionally elected to prosecute the species of Group (A). Applicants herewith affirm this election. Claims to non-elected species have

accordingly been withdrawn, pending their reintroduction and examination upon the Allowance of a generic claim.

III. The Rejection Pursuant to 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 92, 96-101 and 105-114 pursuant to 35 U.S.C. § 112, second paragraph. Claims 98 and 107 have been withdrawn as directed to non-elected species. Applicants have amended claims 92, 96-97, 99-101, 105-106, and 108-114 to address the Examiner's concerns. Support for the amendment can be found at Paragraph No. **0066** of the Specification. Applicants respectfully submit that the rejection may be properly withdrawn in light of such amendment.

IV. The Rejection Pursuant to 35 U.S.C. § 112, First Paragraph

A. The Rejection of Claims 92-96-101, 105-114

Claims 92, 96-101 and 105-114 have been rejected as not enabled by the Specification. Claims 98 and 107 have been withdrawn as directed to non-elected species and claims 101, 105-106 and 108-114 do not contain the term of concern to the Examiner, accordingly, the rejection is believed to apply only to claims 92, 96-97, 99-100. Two bases for the rejection have been advanced by the Examiner: that the claims read upon "***a polypeptide*** comprising a variant Fc region;" and that they recite that the variant Fc region "comprising ***at least*** an amino acid modification." Applicants respectfully traverse and request reconsideration.

1. "*A Polypeptide* Comprising A Variant Fc Region;"

Applicants respectfully submit the claims are fully enabled as to the recitation of "**a polypeptide** comprising a variant Fc region." As the Examiner will appreciate, the Fc region is naturally a portion of an antibody. Accordingly, an antibody is "a polypeptide comprising a variant Fc region." The Application details multiple examples of the production and use of such antibodies. Likewise, the Application discloses that the variant Fc region may be conjugated to a wide variety of molecules (and thus such

molecules would comprise "a polypeptide comprising a variant Fc region"). Such molecules include: monoclonal, bi-specific, multi-specific, human, humanized, chimeric antibodies, single chain antibodies, Fab fragments, $F(ab')_2$ fragments, disulfide-linked Fvs, and fragments containing either a VL or VH domain or even a complementary determining region (CDR) that specifically binds an antigen, in certain cases, engineered to contain or fused to an FcγR binding region (see, e.g., Paragraph No. **0050);** polypeptide cellular ligands (see, e.g., Paragraph No. **00144**); engineered human or humanized antibodies (see, e.g., Paragraph No. **00148**); polypeptide toxins (see, e.g., Paragraph No. **00154**); polypeptide marker sequences (see, e.g., Paragraph No. **00155**), enzymes (see, e.g., Paragraph No. **00157**), antibody conjugates (see, e.g., Paragraph No. **00161**).

In light of the present Application's disclosure of encompassed variant Fc regions, suitable polypeptide conjugates of such variants can be readily produced. In this regard, methods for forming conjugates are well known and are, moreover, referenced in the present Application (see, e.g., Paragraph No. **00160**).

Accordingly, Applicants submit that the rejection of claims 92-96-101, 105-114 pursuant to 35 U.S.C. § 112, first paragraph on the basis that the Application fails to enable the full scope of claims directed to molecules comprising "*a polypeptide comprising a variant Fc region*" having at least an amino acid modification at position 396 relative to a wild-type Fc region, and exhibiting increased affinity relative to a polypeptide comprising said wild-type Fc region, may be properly withdrawn.

2. "Comprising *At Least* An Amino Acid Modification."

Applicants understand the Examiner's rejection to reflect a concern that the present Application fails to provide sufficient guidance regarding amino acid substitutions that may alter antibody function. The Examiner has supported the rejection by citing to Lund *et al.* as teaching that even a single amino acid replacement within the CH2 domain of an IgG can alter the glycosylation profile of an antibody and influence its function, and to Lazar *et al.*, which is stated to show that the determinants of antibody

properties overlap (so that altering a determinant to affect one property may also affect a different property). The Examiner has advised that given the extensive variation permitted by the claims, the invention lacks sufficient predictability. The Examiner has also advised that the Specification fails to provide sufficient guidance as to which residues should or should not be changed to achieve a variant immunoglobulin having a desired function. Applicants respectfully traverse and request reconsideration.

The present claims reflect the discovery that the identity of the residue present at position 396 is an important determinant of the affinity with which an Fc region binds to an FcγR (see paragraph **0043**, for example). Applicants accordingly submit that the claimed invention concerns molecules having two readily ascertainable attributes:

- a variant Fc region comprising at least an amino acid modification at position 396, according to the EU index as in Kabat, relative to the sequence of a wild-type Fc region; and
- a variant Fc region that is able to bind an FcγR with an increased affinity relative to a wild-type Fc region.

It is respectfully submitted therefore that the present Application need do no more than objectively enable those of ordinary skill to:

(A) produce molecules having variant Fc regions comprising at least an amino acid modification at position 396, and

(B) screen amongst such molecules (*without undue experimentation*) to identify those molecules whose Fc region is able to bind an FcγR with an increased affinity relative to a wild-type Fc region.

As discussed in the accompanying Declaration of Dr. Jeffrey Stavenhagen, the present Application indeed provides such guidance.

As Dr. Stavenhagen advises, the Application would have enabled those of ordinary skill to produce polypeptides comprising a variant Fc region comprising at least an amino acid modification at position 396. In this regard, the Application discloses that screening for desired variant Fc regions may advantageously be conducted by forming a library of clones encoding variant Fc regions. Multiple methods for accomplishing this goal are taught (see, e.g., Paragraph Nos. **00176-00183** and **390-392**). The Application further enables such methods by providing deposited clones of suitable Fc regions (see, e.g., Paragraph No. **0055**), and by providing specific working examples of how such libraries are constructed and used (see, e.g., Paragraph No. **0425-00432**). In light of such evidence and such disclosures, it is submitted that the originally filed Specification would clearly have enabled those of ordinary skill to produce a library of Fc variants having at least an amino acid modification at position 396 of the Fc region without undue experimentation.

As Dr. Stavenhagen further advises, the Application would have enabled those of ordinary skill to have easily screened such polypeptides for those having a variant Fc region that is able to bind an FcγR with an increased affinity relative to a wild-type Fc region. In this regard, the Application discloses that surface display technology is preferably employed (see, e.g., Paragraph Nos. **00184-00189** and **393-404**), since it is capable of rapidly and effectively analyzing very large numbers of candidates (e.g., 10^5-10^8) simultaneously. As noted by Dr. Stavenhagen, *even when starting with wild-type Fc region clones*, the methods of the present invention enabled the isolation of polypeptides falling within the scope of the claims. In this regard, the Application discloses that 10^7 different library members can be simultaneously screened (see, e.g., Paragraph No. **00395**), and that when such a screen was performed using a mutated clone of wild-type Fc regions, ***18 of 32*** independent analyzed clones ***(~56%)*** were found to encode polypeptides having a variant Fc region that is able to bind an FcγR with an increased affinity relative to a wild-type Fc region (see, Paragraph No. **00400**). Of 64 variants so identified, ***6 (~10%)*** comprise a modification at position 396. Thus, in sum, *even when*

starting with wild-type Fc region clones, the methods of the present invention fully enable the isolation of multiple species of variants encompassed by the present claims.

The claimed invention, however, enhances such enablement by teaching that a library of variants at position 396 (e.g., P396L) – ***a site that the Application demonstrates affects the ability of an Fc region to bind an FcγR with an increased affinity relative to a wild-type Fc region*** – be created and employed in lieu of a wild-type library (see, e.g., Paragraph No. **00427**). The Application provides methods (and working examples) to enable those of ordinary skill to screen among the members of such a library to identify the subset of molecules falling within the scope of the present claims (see, e.g., Paragraph No. **00425**). The Application discloses multiple different screening approaches for identifying members of this library whose Fc region is able to bind different FcγRs with an increased affinity relative to a wild-type Fc region (see, e.g., Paragraph Nos. **00426-00441**). Of 180 analyzed clones, **19 (~11%)** were found to exhibit this characteristic. Thus, in sum, the methods of the present invention fully enable the predictable and reproducible isolation of multiple species of variants encompassed by the present claims.

The Application further enables the claims by disclosing and characterizing an extensive number of exemplary polypeptides comprising variant Fc regions possessing a non-native amino acid residue at position 396 (such variants are, for example, disclosed in **Tables 2-5**).

Variant Fc					
P396H					
P396L					
P396L	K210M				
P396L	P217S				
P396L	P227S				
P396L	V240A				
P396L	L242F				
P396L	P244H				
P396H	K246T				
P396L	P247S				
P396L	T250A				
P396L	R255L				
P396L	E258D				
P396L	H268D				
P396L	H268N				
P396L	V303I				
P396L	V305L				
P396L	V323I				
P396L	K326I				
P396L	K334N				
P396L	L358P				
P396L	K370E				
P396L	S375C				
P396L	V379M				
P396L	N384K				
P396L	K392T				
P396L	S400F				
P396L	L410H				
P396L	Q419H				
P396L	Q419L				
P396L	V427A				
P396L	K288N	A330S			
P396L	R292L	T359N			
P396L	Y319F	P352L			
P396L	V215I	K290V			
P396L	P217A	T359A			
P396L	K246N	Q419R			
P396L	K261N	K210M			
P396L	K290T	N390I			
P396L	K326I	S408N			
P396L	K210N	K222I	K320M		
P396L	V273I	K326E	L328I		
P396L	F275L	Q362H	N384K		
P396L	K288R	T307A	K344E		
P396L	K290E	V369A	T393A		
P396L	P217S	V305I	I309L	N390H	
P396L	C229Y	A287T	V379M	L443V	
P396L	F243L	V305I	A378D	F404S	
P396L	T215P	K274N	A287G	K334N	L365V
P396L	D221E	D270E	V308A	Q311H	G402D

In sum, as Dr. Stavenhagen declares, the Application discloses fully enabling methods sufficient to permit those of ordinary skill to obtain polypeptides comprising variant Fc regions encompassed by the present claims, and such variants may be readily obtained using only routine experimentation. A large number of exemplary polypeptides comprising such variant Fc regions is disclosed.

Applicants accordingly respectfully submit that the present claims are fully enabled by the specification, which teaches multiple species encompassed by the claims as well as a reproducible, efficient and sufficient method for isolating additional Fc variants. ***In re Wands***, 858 F.2d 731, 736-37 (Fed. Cir. 1988) is considered to be particularly pertinent, since the case not only articulates the proper standard for assessing enablement, but also concerns claims to immunoglobulins. As in ***Wands***, the present Applicants taught an enabling method for obtaining encompassed immunoglobulins, and disclosed a significant number of encompassed species. The Court of Appeals for the Federal Circuit considered the following factors as bearing on the issue of enablement (***Wands***, 858 F.2d at 737):

1. the nature of the invention;
2. the relative skill of the art;
3. the state of the art;
4. the breadth of the claims;
5. the amount of direction or guidance provided by the patentee;
6. the presence or absence of working examples;
7. the quantity of experimentation necessary; and
8. the predictability of the art and the breadth of the claims.

The nature of the invention claimed in the Application relates to complex biotechnology. Thus, the Applicants have provided:

- a very substantial disclosure;
- detailed direction and multiple working examples;
- clones (deposited with the ATCC) encoding Fc regions that may be employed in the disclosed methods;

- the sequence of multiple variant Fc regions encompassed by the claims;
- enabling methods sufficient to permit those of ordinary skill to isolate additional encompassed Fc variants; and
- a showing that such methods can be predictably employed for this purpose.

In light of the very high level of skill of those practicing in the art of the invention, Applicants submit that the present Application enables the full scope of the claimed invention. Accordingly, Applicants submit that the rejection of claims 92-96-101, 105-114 pursuant to 35 U.S.C. § 112, first paragraph on the basis that the Application fails to enable the full scope of claims directed to molecules comprising a variant Fc region comprising "*at least an amino acid modification*" at position 396 relative to a wild-type Fc region, and exhibiting increased affinity relative to a polypeptide comprising said wild-type Fc region, may be properly withdrawn.

B. The Rejection of Claim 114

Claim 114 has been additional rejected in light of its recitation of being a "***pharmaceutical***" composition. The Examiner has predicated the rejection on the conclusion that the Specification fails to adequately teach how to effectively use an antibody pharmaceutical composition. Applicants respectfully traverse the rejection and request reconsideration.

Applicants note the Examiner's reliance upon a footnote in the ***Ex parte Aggarwaal*** opinion as supporting the conclusion that pharmaceutical compositions involving antibodies are unpredictable. Applicants note that ***Aggarwaal*** was written in 1992, and was directed to the state of the art as of ***1984*** (the filing date of the Application under review). It is submitted that whatever the current validity of the legal conclusions provided by the ***Aggarwaal*** opinion, the case does not stand for the proposition that pharmaceutical therapies involving antibodies are immutably or intrinsically unpredictable, despite massive research and development activity. Indeed, whatever the unpredictability of antibody therapies in 1984, they had become well recognized and

conventional as of the filing date of the present Application (see, e.g., Vietta *et al.*, *infra*). Applicants respectfully submit that conclusions as to the predictability of the art of the invention made decades prior to the filing date of the present Application is irrelevant to the patentability of the presently claimed invention. In this regard, the present Application teaches that, as of its filing date, multiple different antibodies were in fact being predictably employed as therapeutic agents (see, e.g., the extensive listing of employed therapeutic antibodies provided on pages 119-122 and on pages 139-144).

The concern indicated in the cited Vietta *et al.* reference does not alter the fact that therapeutic antibody pharmaceutical compositions are indeed well known to the art. Indeed, the reference states that monoclonal antibodies are a multibillion dollar industry, with antibodies currently being used in treatment for a wide range of conditions (see page 308, first paragraph of third column). Thus, the thrust of the cited Vietta *et al.* reference is ***not*** that antibody use is unpredictable, but rather that facts which would have predicted the failure of the specific antibody that is the subject of the article were *ignored* (see page 308, lower paragraph of central column).

It is respectfully submitted that the Examiner's conclusion of unpredictability with respect to the therapeutic use of antibodies is not supported by the art as of the effective filing date of the Application. Accordingly, it is submitted that the rejection of claim 14 pursuant to 35 U.S.C. § 112, first paragraph may be properly withdrawn.

V. The Rejection Relating to Obviousness-Type Double Patenting

The Examiner has advised that certain claims of the present Application conflict with claims of the Assignee's co-pending, non-allowed, United States Patent Applications Serial Nos. 11/271,140 and 11/502,820. A provisional double patenting rejection has accordingly been made.

Applicants respectfully request that the Examiner hold this rejection in abeyance until such time as allowable subject matter is found in this Application and those of United States Patent Applications Serial Nos. 11/271,140 and 11/502,820. Upon the

determination that conflicting subject matter exists with respect to the allowed claims of such Applications, Applicants will respond to any double-patenting rejection by amending or cancelling the conflicting claims, by filing a terminal disclaimer or by such other action as would be warranted and permitted under such circumstances.

VI. Concluding Remarks

Applicants submit that the present response is complete and complies with the requirements of 35 U.S.C. §121. The Application is believed to be in condition for Examination and early notice of favorable action is respectfully requested. Should the Examiner have any remaining questions regarding the subject invention or its patentability, Applicants encourage the Examiner to contact the undersigned to answer such questions or provide any desired additional information.

Respectfully Submitted,

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